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THE PROBLEM OF PRIMARY HYPERPARATHYROIDISM. A CLINICAL STUDY

James A. O'Neill, Jr.

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THE PROBLEM OF PRIMARY HYPERPARATHYROIDISM.

A CLINICAL STUDY

by

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B.S., Georgetown University, 1955

A Thesis Submitted to the Faculty of the
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Introduction and Historical Background

It is the purpose of this report to present a clinical appraisal of primary hyperparathyroidism as it has been encountered at the Yale-New Haven Medical Center. Material was examined with the hope that suggestions might be made for more effective methods of diagnosis and treatment. In this regard some importance has been placed on the natural history of the disease as it has been experienced in this center.

Primary hyperparathyroidism is a disease condition wherein more parathyroid hormone is manufactured than is needed,[5] and this leads to both obvious and obscure pathophysiologic manifestations, Even though the latter statement would be acceptable today, we would necessarily be forced to grant that this knowledge has not been available to us for very many years. It was in 1880 that Ivar Sandstrom gave the first description of the very existence of the glandulae parathyreideae.[2] Gley redescribed them in 1891, and both he and Vessale and Generali in 1896[14] independently performed extirpation experiments to prove that it was the removal of the parathyroids and not the removal of the thyroid that caused the condition called tetany. In 1891, quite unaware of the fact that he was contributing to the field of parathyroid disease, von Recklinghausen described sixteen cases of skeletal disease which he called osteitis fibrosa cystica.[2] Three of these cases are generally accepted as primary hyperparathyroidism, and it is interesting that he described the presence of a large red-brown "lymph gland" in the neck of one of these three patients. Thirteen years later in 1904 Askanazy

reported a case of this bone disease in a woman who also had a tumor of one of her parathyroids[89]. However, this concept had to be reenforced before it was noticed, just as so many other new scientific thoughts. This contribution was made by Jacob Erdheim in 1906 and 1907, who suggested that a relationship existed between the parathyroids and calcium metabolism, because he noted that the teeth of his parathyroidectomized rats crumbled[43], and because there seemed to be an association between osteomalacia, rickets and enlargement of the parathyroids[89]. Schlagenhaufer went a bit further in 1915 and said that single parathyroid tumors could be the primary cause of osteitis fibrosa cystica[86]. The final step came in 1925 when Felix Mandl removed such a tumor from a thirty-eight year old pensioned streetcar conductor who had had white sediment in his urine and clear bones with cysts for four years[74]. The patient improved even though he was destined to be stricken a second time several years later[75]. Such was the European approach to the problem.

In this country as early as 1909 MacCallum and Voegtlin commented on the relationship between the parathyroids, calcium metabolism and tetany[73]. In 1925 Collip actually extracted an active principle from the glands[34], and one year later he found that the serum calcium was elevated in dogs to which he gave excessive doses of his extract[35]. In 1929 Barr and others reported the successful treatment of a case and they used the term hyperparathyroidism for the first time[12]. Although

the case of Captain Martell occurred prior to this it was not reported until a year later. However, the latter case was unique in that it was the first time a sternum had been split to extract the offending tumor from the mediastinum[52]. The history of contributions to the understanding of this disease is far more extensive than the outline given here, and certainly more information is being accumulated.

From the physiologic point of view we know of two actions of the parathyroid hormone or hormones, and it is granted that there may be actions other than these. Albright and Reifenstein believed that excess hormone somehow made phosphate more readily excreted by the kidney and upon this there followed a derangement of the calcium-phosphorus equilibrium and subsequent resorption of calcium-phosphate salts from the bone[4]. It is now known that parathyroid extract acts directly on bone and causes it to release calcium salts[11,30,31]. Second, the hormone acts on the kidney and inhibits the tubular reabsorption of phosphate so as to increase the clearance of phosphate and to decrease its level in the serum[51,61,71]. These are the more generally accepted mechanisms, but there are certainly numerous other theories still being considered. For example, a recent report suggests that magnesium chloride and potassium chloride are capable of desensitizing the body to certain toxic effects of the parathyroid hormone, particularly its ability to cause soft tissue calcification[88]. More information about the pathophysiology and etiology will be presented as the case studies unfold.

The Natural History of Hyperparathyroidism from the Clinical Point of View

In the period from 1931 through 1958 the diagnosis of primary hyperparathyroidism has not been commonly made at this center. During this time 25 cases have been encountered at the Yale-New Haven Medical Center, and in all but one of these the diagnosis was proven by microscopic examination of tissue found at surgery or autopsy. Reference will also be made to six cases in which the diagnosis was highly probable but not proven because of insufficient follow-up or for other reasons. In an additional five cases definite parathyroid adenomas were found at postmortem, but it was impossible to make a clinical evaluation of these cases. It has been pointed out in several reviews that many more diagnoses have been made in recent years[25,57,66]. However, this has not been the case at our center. Of the 25 cases, ten were seen between 1931 and 1939; five were seen between 1940 and 1949; and the last ten were seen from 1950 through 1958. It is interesting that no cases were diagnosed or treated from 1941 through 1944, which were the World War II years for the most part. One might speculate that physicians interested in this problem were away, or that during war years people might be less apt to present themselves with some of the seemingly minor symptoms that these patients often experience.

Considering the size of other series, this condition is probably more common than the size of this study indicates. However, no estimate

has been possible as to the actual incidence of hyperparathyroidism. It has been suggested by Wilder and Howell that a greater incidence of the disease is to be found in the North Atlantic states and Scandinavia than in some other areas[96]. They postulated that embryonic cells or cell rests in response to a lack of vitamin D proliferate to form an adenoma which is often functional, and the geographic distribution follows since persons living in these areas presumably get less sunshine. Although most authors indicate that more women have hyperparathyroidism than men[5,25,79,93,96] some studies suggest that the sexes are affected equally[17,82]. In this study there were 13 females and 12 males, but weight must be placed on larger series of patients and most of these show a preponderance of females.

It has been demonstrated that hyperparathyroidism may occur at almost any age from childhood to old age, but it is most common in the thirty through fifty age group[53,96]. This group agrees essentially with this statement. The range of ages in the females was 28 years through 72 years of age, and in the males from 37 to 82 years of age. The average age of both groups was 48 years and most cases fell between the ages of 35 and 55. There were only two cases over the age of 67, one of which was 72 and the other 82 years of age. It is rare to find the disease in patients this old; however, the data indicate that they probably had it for many years before the diagnosis was made.

With respect to the duration of symptoms, it must be said that

duration means the length of time between the onset of symptomatology and surgical treatment or death. This is obviously inaccurate since the disease may have been present long before symptoms began. However, this is some indication of our progress in diagnosis so it is useful. The ultimate aim, of course, is diagnosis as early as possible so as to avoid complications which may become chronic. Renal involvement is important in this respect since hypercalcemia, which is present from the beginning, leads to precipitation of lime salts in the cells and lumen of the proximal convoluted tubule, and this takes place in a ground substance of mucoprotein possibly derived from bone matrix[57]. This is a continuous process unless its underlying cause is stopped. The duration of symptoms in this group varied from six months to 29 years with an overall average of five years and ten months. Hellstrom gave similar figures[58]. Shelling has pointed out that renal involvement due to precipitation of calcium salts usually becomes apparent before involvement of bones[90], and more recent studies indicate that as the diagnosis is being made earlier now, less and less patients are being seen with bone disease[25]. In this study, those with only evidence of renal disease had an average duration of symptoms of five years and ten months while those with bone disease as well had their symptoms about a year longer.

Hyperparathyroidism is noted for its multiplicity of symptoms, some of which may be quite obscure, especially when they occur alone. However, some order may be made from all this and symptomatology

may be considered from the standpoint of etiology and of occurrence in time. Chronologically, the disease may be divided into the period of inception, the period of early complications, the period of advanced complications, and the period of irreparable and lethal damage. Most authors consider this same thing in another manner by discussing symptoms of hypercalcemia, which can occur throughout the four above-mentioned periods, renal symptoms, and symptoms of bone disease. The latter two can occur separately or together, but, as we have already seen, renal disease usually precedes bone involvement, which may never occur depending upon the patient's diet. These considerations are important since the amount of renal damage present seems to determine the ultimate prognosis[56]. While the bone disease will regress, nephrocalcinosis and renal damage will not.

Symptoms and their frequency must be considered in the light of which disease processes are in prominence. For example, the 25 patients in this series had the following: one patient had only mild osteoporosis; one patient had osteitis fibrosa cystica and minimal renal involvement; five had only renal disease; five more had renal disease plus osteoporosis; twelve had renal disease and severe bone disease; and one patient had no evidence of renal impairment or bone disease. The large number of patients seen during the period from 1931 to 1939 would probably explain the large number of patients with significant bone disease. The patients seen most recently would not be expected to show as great

an incidence of skeletal involvement.

With respect to signs and symptoms, stress was originally placed on bone disease[13]. Later, signs of renal dysfunction such as polyuria, azotemia and calculi were recognized[50]. Even though the occurrence of gastrointestinal symptoms was recognized early[3], it was not until more recently that the frequency of them was appreciated[93]. In fact, St. Goar urges that gastrointestinal symptoms are clues to early diagnosis and that common complaints such as constipation and intractable peptic ulcer should be worked up with the diagnosis of hyperparathyroidism as one of the possibilities. In this study a large number of patients (ten) had chronic constipation, and two or eight percent had peptic ulceration. This agrees substantially with the work of others[3,25,78]. These and other gastrointestinal symptoms such as anorexia, nausea and vomiting are believed to be due to visceral atony secondary to hypercalcemia[93]. There was one instance of pancreatitis postoperatively which Cope believes is due to hypercalcemia which leads to the formation of pancreatic calculi, ductal obstruction and pancreatitis[36]. After removal of the parathyroid tumor this type of pancreatitis tends not to recur. Steatorrhea is also mentioned as a rare associated symptom[39].

A large number of patients had symptoms and signs referrable to the skeletal system, but this reflects the disease as seen 20 years ago for the most part. Eight patients had spontaneous fractures; thirteen had pain in the lower extremities; ten had other bone or joint pain; and

six had spine deformities. The patients who had severe skeletal disease also had the most severe damage.

In this study, as in just about all others, the most prominent symptoms were those related to renal disease. Polyuria, in particular, is a common finding in hyperparathyroidism, and it is thought to be due to a loss of function of the second part of the distal tubule and of the collecting tubules which diminishes the reabsorption of water. This is independent of obvious structural damage[33]. Polyuria and polydipsia occurred in nine patients; nocturia, pyelonephritis and demonstrable calculi in twelve, and renal colic in fifteen patients. Fifteen patients had hypertension ranging from 130/95 to 230/140. Of these, twelve had disturbance of renal function manifested by a nonprotein nitrogen (NPN) over 40 milligrams percent or a phenolsulfonphthalein (PSP) excretion of 60 percent or less in two hours. Fourteen of the above-mentioned patients who had infection and/or stones had hypertension, but only ten of these had measurable signs of impaired renal function. Although the degree of renal damage seems to be related in a major way to the presence of hypertension, it does not appear to be the only factor since some of those with severe infection or renal stones, who did not have measurable renal damage, also had hypertension. Four additional patients had signs of renal failure.

This series also demonstrates a high incidence of some of the more

general symptoms. Nine patients had weight loss of ten pounds or more in the year before treatment, and twelve patients had severe lassitude and fatigue. As a consequence of hypercalcemia, eleven patients complained of muscular weakness; nine had arterial calcification; and one had calcification of the soft tissues of his fingers. One patient died of a dissecting aneurism of the aorta which was heavily calcified. There were no instances of band keratitis or calcification in the lungs, stomach, or cerebral hemispheres[62,70]. Three patients had mental changes characterized by confusion, anxiety and irrationality[44]. These changes are believed to be due to hypercalcemia and all three patients had average serum calcium levels above 13 milligrams percent. Three patients had evidence of a hypochromic anemia, but in addition to the expected bone disease which supposedly encroaches on the marrow space[18], these patients also had evidence of impaired renal function which confuses the issue. Only two patients had electrocardiographic evidence of shortening of the QT interval although it is supposedly quite common[68].

Up to this point, the manifestations discussed have been those of a chronic nature. One of the more interesting aspects of hypercalcemia and hyperparathyroidism is that the disease may assume an acute form. Hewson has reviewed this problem and he points out that most cases are acute exacerbations of chronic parathyroid disease and that a high calcium intake and immobilization seem to play a part[60]. It may also be precipitated by stress such as surgical procedures, and in one reported case it

occurred in a patient who had a biopsy of the submaxillary gland[62]. It is characterized by the sudden onset of anorexia, nausea, vomiting, weight loss, drowsiness, abdominal pain and azotemia. Impaired renal function and also electrocardiographic findings of a shortened QT interval and virtual disappearance of the ST segment are characteristic. One mechanism of death is cardiac arrest in systole. This center has had experience with one such case in a 39 year old man who presented because of the sudden onset of severe epigastric pain, nausea, vomiting and diplopia. It took a few days to establish the diagnosis of hyperparathyroidism and during this time the patient's condition deteriorated rapidly; he became more and more obtunded and his NPN rose steadily to 122 milligrams percent. His serum calcium levels ranged between 13 and 20 milligrams percent and the serum phosphorus between 3.7 and 5.4 milligrams percent. Surgery was performed as soon as the patient could be prepared properly and a large chief cell adenoma weighing 7.9 grams was found. Postoperatively the man did well with remission of all symptoms and a return of his NPN to normal levels. It should be noted that he had had symptoms of parathyroid hyperfunction for at least a year before his acute attack. This patient might very well have died from this process had it not been recognized.

The clinical behavior of hyperparathyroidism may be unique in another manner, and that is that a patient may present with other endocrine gland adenomas. Underdahl and his colleagues have reported eight

cases in which there was an association of adenomas in the parathyroids, pituitary and pancreatic islets[94]. Of the 25 proven cases here, four had thyroid adenomas as well as parathyroid adenomas, and one of these also had a coexisting pheochromocytoma, an association which has not been reported to my knowledge. There was also one case in which there was an associated basophilic pituitary adenoma.

The lesson to be learned from a discussion of the natural history of hyperparathyroidism from the clinical point of view is quite simple. Our aim is early diagnosis and treatment so as to avoid permanent sequellae and this will only follow if we have a high index of suspicion when certain signs and symptoms are presented to us. Renal symptoms lead the list and suggestive manifestations would be polyuria, polydipsia, nocturia, renal colic, infection, hypertension and calculi. Hellstrom reviewed the subject of calculi and stated that hyperparathyroidism probably exists in from three to eight percent of those with renal stones[55]. In this study 92 percent of the patients had some renal symptoms. Although 76 percent of the patients had skeletal symptoms, the incidence should become less. However, bone pain, especially in the legs, pathologic fractures, giant cell tumors, and the development of kyphosis should be followed up with diagnostic tests. Unexplained weight loss, lassitude and fatigue should make one include this disease in the differential. Gastrointestinal symptoms such as chronic constipation, abdominal pain, nausea and intractable peptic ulcer are early manifestations which should

be a help as well. Sixty percent of the patients here had such symptoms. Finally, any persons with any evidence of soft tissue calcification, especially the young or middle-aged, should be subjected to diagnostic tests. If the large increase in the number of diagnoses made in recent years by other groups is to be taken seriously, the attitude at this center should be that diagnoses are being missed and that the index of suspicion should be higher.

TABLE I.

FREQUENCY OF PARTICULAR SYMPTOMS OR SIGNS

General Symptoms	No. of Patients	Incidence
Weight loss (10 lbs. in past year)	9	36%
Lassitude and fatigue	11	44%
Hypochromic anemia	3	12%
Symptoms Due to Hypercalcemia		
Hypotonia and muscle weakness	11	44%
Chronic constipation	10	40%
Abdominal pain (epigastric)	4	16%
Anorexia	4	16%
Nausea and vomiting	4	16%
Peptic ulceration	2	8%
Abnormal EKG	3	12%
Arterial or other calcification	10	40%
Mental changes	3	12%
Parathyroid crisis	1	4%
Renal Symptoms		
Frequency	2	8%
Polyuria and/or polydipsia	9	36%
Nocturia	12	48%
Pyelonephritis	12	48%
Renal colic	15	60%
Renal, ureteral, or vesicle calculi	12	48%
Hypertension	15	60%
Renal failure	4	16%
Skeletal Symptoms		
Fractures	8	32%
Kyphosis and collapse of vertebrae	6	24%
Leg pain	13	52%
Spine, other bone, or join pain	10	40%

TABLE II.

INCIDENCE OF GROUP SYMPTOMS

Gastrointestinal	60%
Renal	92%
Skeletal	76%

Diagnostic Methods and Differential Diagnosis

Over the years a number of diagnostic tools have been brought into existence, but the perfectly reliable and specific test has yet to be invented. This leads to the unfortunate conclusion that, in many cases, especially the early ones, it may be extremely difficult to substantiate the presence of parathyroid hyperfunction. Probably the most important diagnostic aid is a high index of suspicion in the first place giving careful attention to a history of any of the signs or symptoms mentioned in the section on clinical behavior. Vigorous follow-ups are a necessity.

With relation to the clinical history, radiologic examinations are of some help in establishing the degree of development of the disease and, as such, are adjuncts if we are cognizant of the natural history of hyperparathyroidism. In 1931 Camp and Ochsner and more recently Pugh outlined the various roentgenologic findings seen in this disease, most of which logically follow upon a consideration of the pathophysiology involved[27,81]. One of the signs not mentioned as a usual finding is absorption of the terminal phalanges of the hand with clubbing which is not of the usual type[41]. The pulp of the fingers appears flabby and the finger tips are shortened. The findings in this series are outlined in Table III and the relative frequency of these findings is, for the most part, what would be expected. It is interesting that only two patients demonstrated subperiosteal bone resorption on hand films even though it is

supposedly a dependable and important finding which occurs only in primary and secondary hyperparathyroidism[80]. In fact, unless cysts are present which cause pathological fractures, Pugh recommends that only the hands, teeth, and skull be examined roentgenologically[81]. In the same manner, only one patient had loss of his lamina dura on dental films. As an incidental finding, three patients had single large or small bowel diverticula. Radiologic examination of the neck and mediastinum with barium swallow can often be of help in locating the position of an adenoma preoperatively if it is of sufficient size and is in such a position that it impinges on the trachea or esophagus, or if it contains calcium[98]. The experience at this center has been such that six examinations yielded information while seven did not, so it is a helpful aid both to the diagnostician and the surgeon.

The laboratory diagnosis of hyperparathyroidism leaves something to be desired, but a combination of tests is usually successful. The oldest and still most useful method of diagnosing primary parathyroid hyperfunction is the determination of the serum calcium and inorganic phosphorus levels. Serial determinations which show an elevated serum calcium (normal 9.6 to 11 milligrams percent) and a depressed serum phosphorus (normal 3.5 to 4.2 milligrams percent) are considered to be diagnostic. Since the serum calcium is a measure of the ionic as well as the protein bound calcium, the serum proteins must always be determined as well since aberrations in these are directly proportional to

aberrations in the serum calcium, although the converse is not true. A low serum protein could conceivably conceal a truly elevated serum calcium. Recently it has become evident that more cases are appearing with a normal serum calcium level, possibly due to dietary factors so that calcium levels of 10.5 milligrams percent are now considered elevated[25]. The inorganic phosphorus is not affected this way so more stress has been placed on the significance of a low serum phosphorus, but even this is not always dependable; and then too, if renal failure ensues, the level is usually raised[29]. These difficulties caused investigators to look elsewhere and besides this, even an elevated serum calcium is not pathognomonic. The Sulkowitch test is merely an aid in diagnosis but it is not specific enough[10]. The same is true of balance studies. Placing a patient on a low calcium diet and then following his urinary excretion of calcium is a helpful test, but it does not differentiate hyperparathyroidism from other hypercalciurias, and it is also not helpful when there is renal insufficiency[20]. The phosphate deprivation test operates on the principle that the derangements of the disease will be accentuated by a low intake of phosphate, but skeletal and muscular release of endogenous stores often confuse the results[48]. Results with the calcium tolerance test[64] are often not what would be expected in hyperparathyroid subjects and a normal response is not inconsistent with the diagnosis[48]. Also, this test must not be used in patients with cardiac or renal disease or in patients with high serum levels of calcium

TABLE III.

FREQUENCY OF PARTICULAR X-RAY FINDINGS

	No. of Patients	Incidence
Generalized osteoporosis	15	60%
Bone cysts	9	36%
Fractures	8	32%
Giant cell tumors	1	4%
Clubbing	1	4%
Gramular appearing skull	9	36%
Subperiosteal bone resorption	2	8%
Loss of lamina dura	1	4%
Calcified soft tissues	10	40%
Nephrocalcinosis	8	32%
Renal, ureteral, or vesicle calculi	12	48%
Bowel diverticulum	3	12%
Peptic ulceration	2	8%

because of the danger of crisis[29]. The cortisone test depends on the fact that an elevated serum calcium due to hyperparathyroidism will not be lowered by the administration of cortisone[40]. It is not particularly helpful when the serum levels of calcium are not elevated. More recently, stress has been placed on measurement of phosphate clearance expressed as a ratio of the clearance of phosphorus to the clearance of creatinine (C_p/Ccr) and emphasis has also been placed on a related measurement, the percentage of tubular reabsorption of phosphate (TRP)[71,84]. There are difficulties due to variations of clearance in the same individual and also because of difficulties concerned in the mechanics of the test, but these are probably the most useful tools available now. If renal failure is present however, the latter two tests are of dubious value[71]. Alkaline phosphatase, NPN and PSP excretion tests are useful in assessing the degree to which the disease has developed. There are several other tests but the latter are the main examinations in common use, and there are also tests in the process of development.[42]

In this study the determinations of the serum calcium and phosphorus levels were the most reliable criteria for diagnosis. The average preoperative serum levels in 24 patients with essentially normal serum proteins was 13.41 milligrams percent of calcium and 3.14 milligrams percent of phosphorus. The one patient who did not have determinations preoperatively was thought to have a thyroid nodule. Average calcium levels were above 12 milligrams percent in all but four patients. In two

of the four in whom the average serum levels were 10.91 and 10.27 milligrams percent, serial determinations showed that the levels were elevated. In a third patient who had an average of 10.28 milligrams percent, the average serum phosphorus level was 1.9 milligrams percent and it was also low in one of the two latter patients. The fourth patient whose serum calcium and phosphorus levels were 9.56 and 4.84 milligrams percent respectively had only one determination before death. The average serum phosphorus was 3.14 milligrams percent with levels above 3.50 milligrams percent in only six patients, all of whom had evidence of severe impairment of renal function. In every case, if available serial determinations were studied the diagnosis of parathyroid hyperfunction was strongly indicated.

Specialized studies were performed on only four patients in this series and all four had characteristic serum findings. McGeown defines the normal range of the C_p/Ccr ratio as less than 10 percent[77]. One patient had a ratio of 18.49 and 21.77 percent on two determinations. Urinary balance studies were within normal limits and a calcium tolerance test was compatible with the diagnosis. Another patient had a Cp/Ccr of 33 percent and a 24 hour urinary excretion of 200 milligrams, which is over twice the normal. A third patient had a C_p/Ccr of 31.38, 29.35, and 30.95 percent on three determinations with a normal 24 hour excretion of phosphorus. The last patient had a C_p/Ccr of 14 percent with a normal TRP. A cortisone test was compatible with the diagnosis. Obviously, not enough experience has been gained in the use of these studies

but they are certainly worth the effort. This is especially true with regard to the TRP determination. Serial serum examinations are extremely valuable, but a combination of some of the more specialized tests may be helpful. It would seem that chemical tests are the only real basis for early diagnosis and treatment, especially when serum levels of calcium and phosphorus are ambiguous.

Additional Cases

In six cases other than the 25 already discussed, diagnosis is probable although not proven. Case I is a 73 year old woman with hypertension, recurrent renal calculi, and pyelonephritis but no bone disease. Serum calcium is elevated and phosphorus depressed. She has a 24 hour urinary calcium of over 200 milligrams while on calcium restriction and her C_p/Ccr is 26.4 percent. Neck exploration was negative and she is awaiting a mediastinal exploration. Case II was a 54 year old female with renal lithiasis, fatigue, an increased serum calcium and a depressed serum phosphorus. She was lost to follow-up. Case III is a 22 year old male with renal calculi, pyelonephritis, hypertension, elevated serum calcium and depressed phosphorus who is still being followed. Case IV is a male of unrecorded age who had nephrocalcinosis and typical serum findings. Surgical exploration was negative and he has since been lost to follow-up. Case V is a 56 year old female with hypertension, nephrocalcinosis and osteoporosis, soft tissue calcification, typical serum

findings, but a normal C_p/Ccr. Neck exploration was performed and tissue was removed but pathologic examination was inadequate except to say that the specimen was parathyroid. Serum values became normal after operation. The sixth case is that of a 74 year old female with hypertension, osteoporosis, bone cysts, elevated serum calcium and low serum phosphorus. She was unsuccessfully operated on twice with no change after the first procedure but reversal of serum findings after the second neck operation. In this case one might well postulate necrosis of an unseen adenoma due to surgical trauma. This is not unknown and seems likely in this case[63]. These are all cases in which more extensive laboratory work-ups might have been of value. One final form of the disease which we have not experienced is intermittent hyperparathyroidism[95]; and, here too, the laboratory might be helpful.

Differential Diagnosis

The differential diagnosis involved in hypercalcemia and hyperparathyroidism should not be a difficult matter if all aspects of the diagnostic work-up are considered. One of the prominent confusing disorders is the milk-alkali syndrome but history and the absence of hypercalciuria and hypophosphatemia should make the differential[26]. Hypervitaminosis D resembles hyperparathyroidism very closely but the history of excessive intake is helpful and also there is often very extensive soft tissue calcification, more extensive than that seen in hyperparathyroidism[6].

Multiple myeloma may be ruled out by the presence of Bence Jones protein in the urine or of myeloma cells in the bone marrow. Also, the alkaline phosphatase is normal in multiple myeloma whereas it would be elevated in hyperparathyroidism with bone findings[76]. Prolonged immobilization also produces hypercalcemia but the history, normal serum phosphorus and normal alkaline phosphatase differentiate it from parathyroid disease[21]. Sarcoidosis produces tremendous proteinemia and any osseous changes which occur are usually limited to the hands and feet[7]. History of testosterone administration or obvious historical features of various endocrine disorders such as thyrotoxicosis should rule out some other causes of osteoporosis. Metastatic cancer to bone may also give suggestive findings but demonstration of a primary tumor would be the basis of the differential. Tumor without metastasis has also been reported to cause confusion with the postulation that some tumors may produce a parathormone-like substance[85]. Again, the demonstration of such a tumor would be crucial. These are the main differential diagnoses although there are additional causes of hypercalcemia which simulate hyperparathyroidism, but careful attention to details of history and laboratory findings should make the differential without difficulty even in the early cases.

Pathology

By 1935 it had become evident that the pathology of hyperparathyroidism was a complicated matter with respect to the parathyroid glands themselves. In that year Castleman and Mallory gave an extensive description of what histology might be found and they presented a classification[28]. Three general categories are now known. The first group would be by far the most common type of pathology encountered, adenomas. Both Castleman's and Black's experiences are in agreement and their figures state that adenomas are to be expected in about 89 percent of cases[15,28]. Eighty percent will be solitary and the remainder will be multiple. Histologically, over 90 percent of the adenomas will be of the chief cell type or variants and a small number may be Wasserhelle (water-clear) cell adenomas. The latter sometimes cause difficulty in that the surgeon is confronted with the problem of differentiating an adenoma from generalized hyperplasia, the second most common type of pathology, which is present about ten percent of the time. Even though it is usually the case with an adenoma that the uninvolved glands are atrophic, this distinction is not always an easy one[97]. Hyperplasia involves enlargement of all four glands with a predominance of one cell type. Wasserhelle hyperplasia is the most common type but chief cell hyperplasia does occur. The last category is that of carcinoma of one gland accounting for about one percent of cases. Besides having certain histologic appearances, a carcinoma enountered in the course of surgery

is found to be densely adherent to adjacent structures whereas an adenoma is usually able to be shelled away with ease. The primary manifestation is invasion of contiguous structures, and remote metastasis most often is to the lungs or liver, although it is late[92]. On this account, Cope advises that an enlarged densely adherent gland should be removed in toto rather than subtotally for biopsy at operation[37].

The normal parathyroid weighs from 30 to 40 milligrams[46] and measures 6 to 7 millimeters x 3 to 4 millimeters x 1.5 to 2 millimeters[23]. According to Black, adenomas may range in weight from normal to 100 grams or more. In cases with hyperplasia, the total weight of resected tissue in the Mayo Clinic series ranged from 1.4 to 52.5 grams[16]. Also, in hyperplasia the color of the tissue is characteristically chocolate brown whereas in adenomas the color usually is dark red brown, but this varies with the amount of fat present. The relative location of these tumors will be discussed later.

In this series 24 patients had demonstrable pathology. In the case of one additional patient, although no pathology was found at two operations, the diagnosis was felt to be definite on clinical and laboratory grounds. Twenty-two patients had the diagnosis proven at surgery and two at autopsy. Twenty-two patients had a total of 25 adenomas with 3 of these having two adenomas each. Two patients each had a single Wasserhelle adenoma and 20 patients had chief cell adenomas or variants of this. One patient had primary Wasserhelle hyperplasia involving all of his para-

thyroids and one patient had a carcinoma without local or distant metastasis. The latter patient was treated elsewhere and has been reported[45]. This clinic has followed this patient and he is now doing well over four years after surgery. Percentage-wise, 92 percent of patients had adenomas, 80 percent being solitary and 12 percent double. Four percent had primary hyperplasia and the same amount had carcinoma. These figures essentially agree with what might be expected although the series is too small to be statistically valid in its entirety.

The adenomas found in this group of patients ranged in weight from 341 milligrams to 8 grams with an average of 3.2 grams. The size varied from 10 x 6 x 5 millimeters to 25 x 25 x 25 millimeters with an average of 25 x 16 x 10 millimeters. None of the adenomas fell within the range of normal but about 25 percent of them were small enough to be expected to cause difficulty at surgery. For the most part, the smaller tumors were found more recently so if cases are being diagnosed earlier it will have to be accepted that the surgical treatment will be more challenging. According to Castlemen there is a correlation between the size of an adenoma and the level of the serum calcium[28]. In this study this only held true when the tumors were as large as five grams or more. The carcinoma measured 40 x 30 x 10 millimeters and three of the glands found in the patient with hyperplasia averaged 24 x 18 x 10 millimeters. Only nine of the 24 patients had clinically palpable pathology preoperatively so the absence of a neck mass certainly means nothing as far as this disease is

concerned. In fact, it has been said that in a hyperparathyroid patient, a palpable nodule in the thyroid area usually turns out to be a thyroid nodule[49].

Treatment

The only accepted treatment of primary hyperparathyroidism is surgical[24]. Albright and Reifenstein have reviewed other approaches to treatment and also came to this conclusion[8]. High calcium or phosphate intake enhance the disease process, but restriction of the latter and hydration are of some help in preparing a patient for surgery. X-ray irradiation has been tried in the past, but this is generally believed to be inadequate and no convincing reports of successful x-ray treatment are available. Over the years the surgical approach to the problem has not changed a great deal since it has been based on the anatomy and embryology of the glands.

The surgery for parathyroid hyperfunction is not an easy matter. The main problem is to find the glands, and this is difficult if they are small or abnormally located. Reference has already been made to the appearance and size of both normal and pathological glands, but it should be noted again that about 25 percent of the adenomas found in this series were small enough to be considered hard to find. As far as location is concerned, Gilmour states that over 90 percent of the superior glands are located above the lower third of the thyroid on its posterior or medial surface and that 95 percent of the inferior glands are located in the vicinity of the inferior poles of the thyroid with an additional three percent between three and six centimeters below the level of the thyroid[47].

Kirk recently reviewed the embryology of the parathyroids and stressed the possibilities of anomalous position[69]. Such anomalous position may be found anywhere from the upper border of the larynx in the neck to the level of the diaphragm in the mediastinum, and adenomas have been found within the pericardium. Embryologically, tumors may be found anywhere between the bounds of the prevertebral fascia posteriorly and the deep layer of the middle cervical fascia anteriorly[32]. The inferior glands may be found within the thymus. Rare true intracapsular intrathyroid position has been found; it is usually the case that an intrathyroid adenoma is wedged into a sulcus. Kirk also stressed the point that adenomas displaced by migration will all have a vascular pedicle from the inferior thyroid artery whereas if it is anomalous placement by development it will have local blood supply. The latter type will only occur in the anterior mediastinum according to Black[23]. From Gilmour's studies and also from Black's experience, one would expect to find parathyroids through a cervical approach in over 95 percent of cases, and although about seven percent had mediastinotomy in Black's series, it was probably necessary in less than two percent.

As far as the technique itself is concerned, several excellent reviews of the subject have been written already by Chruchill, Cope, Black, Hellstrom, Rienhoff and others[24,32,38,59,82]. The latter two differ from the group in that they feel that if it is decided to do a mediastinal exploration, it should be done as soon as possible. The others concur in

the belief that about a three months' interval should be allowed just in case the neck dissection might have caused necrosis in a tumor not seen at operation. However, considering the fact that only about two percent of cases should require mediastinal exploration, very careful study should be made of the neck dissection first, and one might wonder if re-exploration of the neck might be more fruitful than mediastinotomy after one neck exploration. It certainly behooves the surgeon to be completely familiar with the anatomy and embryology involved, and Cope[38] suggests that this knowledge should be gained at the postmortem table. In addition to the surgeon, however, an experienced pathologist must be available to interpret frozen sections taken at the time of surgery.

In this series of cases 23 patients had surgery performed and in all but one, pathology was found. In this one patient difficulty was encountered in locating the parathyroids and 17 days later a sternotomy was performed with negative results. The patient still had definite evidence of hyperfunction and was referred elsewhere for possible further surgery. It would seem that it might have been well to do more extensive cervical dissection in this case before attempting sternotomy. Also, ideal procedure would have been to identify three atrophic glands in the neck as well as the absence of an adenoma which would presumably have been located in the mediastinum[24]. In the 19 patients with single adenomas and three with double adenomas the locations were predominantly in the neck. Three were found in the right upper gland, four in the left upper;

seven were found in the right lower gland, and two of these were misplaced. One was in the anterior superior mediastinum just below the sternal notch and one which required mediastinal exploration was found in the posterior superior mediastinum between the trachea and esophagus. Ten adenomas were found in the left lower gland. One more was found on the right but it could not be determined whether it was the superior or the inferior gland. Hence, 71 percent of the adenomas were in the lower glands and only one could not be reached through the cervical incision. Twelve adenomas were found on the right and 13 on the left. One patient was found to have two hyperplastic glands at surgery which were removed. She died of pneumonia on the second postoperative day and at autopsy another hyperplastic gland was found in the posterior superior mediastinum between the trachea and esophagus and behind the carotid sheath. The fourth gland was never found. Ideally, one would identify all four hyperplastic glands at operation and remove all but a portion three to four times normal size in order to avoid severe tetany[24]. In the one case with carcinoma, the gland was found in the right inferior position and it was densely adherent to local structures. As mentioned before, adherence forebodes carcinoma, and it is better to remove such glands completely rather than to perform biopsy first. Biopsy of regional lymph nodes should be performed and, if positive, a neck dissection should be done on the side of the lesion. Careful follow-ups should be made as well. It is undecided whether radical dissection in

the absence of palpably enlarged nodes is of any value.

As one can see from what has been said, there are several reasons for failure in treating hyperparathyroidism. If the surgeon is not completely familiar with the problem, his dissection will be inadequate. If he does not identify as many glands as possible, he will miss multiple adenomas or generalized hyperplasia. Even with good technique a surgeon may miss adenomas within the thymus or thyroid or those behind the esophagus, especially if the tumors are soft. Hellstrom suggests that the position is very rarely indicated by x-ray, although our results have been more successful; and he suggests that the surgeon should do Hamilton's test for parathyroid hormone on the blood from both innominate veins with the hope that at least the correct side will be indicated by a higher level of hormone[59]. This has not been evaluated. Other methods of locating tumors have been tried but not with a great deal of success. The application of subclavian arteriography was introduced by Seldinger[87], and Aird and his group have suggested the use of inferior thyroid arteriography at the time of operation[91]. More experience will have to be gained in this regard, but Wyndham already feels that if the adenomas are shown by arteriography, they are probably large enough to be seen anyhow[99]. It would seem logical, however, that such techniques might be useful when glands could not be found at the time of neck dissection because of anomalous location. Still and all, the best aid is painstaking, bloodless dissection of the neck primarily, with

close attention paid to the details of embryology, color and topography.

One final word should be said about the treatment of acute hyperparathyroidism. Since this is a fast-moving and potentially fatal form of parathyroid dysfunction, it is felt that surgery should be performed on an emergency basis, preferably with some preparation by hydration[65]. Hewson suggests that chelating agents such as EDTA may be helpful in lowering the serum calcium prior to surgery[60]. Probably the greatest help would be awareness of such complications as crisis and then rapid initiation of treatment once the process became evident.

Results of Surgery and Complications

In general it can be said that the postoperative course of a patient who has had a parathyroid adenoma removed is a benign one. Gastrointestinal symptoms clear up for the most part[9]. In a day or two after removal of the adenoma, the serum calcium falls to normal levels and the serum phosphorus rises in most cases, but if bone disease is present, the serum calcium may fall to subnormal levels[93]. The bones will recalcify although cysts will remain[19]. Even though rare cases of improvement of renal function have been reported postoperatively[63], nephrocalcinosis and renal damage are considered to be irreversible. This latter fact leads to a very serious complication and that is rapid progressive renal failure. In St. Goar's series three patients with high serum phosphorus levels and NPN's over 40 milligrams percent went into renal failure postoperatively[9]. This is not uncommon, and it is known that renal damage and hypertension will continue to pregress[56]. Part of the explanation for rapid progressive renal failure postoperatively might be the oliguria which occurs during the first 24 hours caused by the sudden withdrawal of parathormone which has a polyuric effect. Black suggests that adequate hydration be given parenterally during the first 24 hours on this account[22]. Rienhoff has also pointed out that soft tissue calcification remains even after successful removal of a tumor[82].

Complications due to operative trauma are not unknown and call for

strict adherence to careful technique. These difficulties would include damage to the recurrent laryngeal nerve with vocal cord paralysis which occurred in two of our cases, and also rough handling of tissues causing destruction or hemorrhage into remaining parathyroid tissue with subsequent tetany. Tetany is a special problem in itself. Some symptoms of hypoparathyroidism following removal of an adenoma are common. They take the form of tingling of the hands and feet, and Trousseau and Chvostek signs are positive. If too much tissue has been removed or if severe bone disease was present, severe tetany may ensue and lead to death. Treatment must be rapid and it has been suggested by Lichtenstein and Levy that 100 cc. of 10 percent calcium gluconate in 1000 cc. of dextrose in N/2 saline be given intravenously. For maintenance of patients with chronic symptoms, they recommend AT 10, one to three cubic centimeters daily until a three plus Sulkowitch reaction is obtained and then one cubic centimeter three times weekly; vitamin D_2, 50,000 to 300,000 units daily; aluminum hydroxide, 30 cc. four times daily; and calcium lactate, 10 grams orally three times daily[72]. Serum calcium levels are followed as well of course. Now that drug therapy is available, tetany is less of a worry. In one of the cases in this hospital's series, a portion of an adenoma was transplanted into the right Latissimus dorsi muscle. Nine months later it was removed and found to be non-functional, and it is impossible to say whether it was ever functional since serum calcium levels came up slowly postoperatively after a big drop and maintained

themselves at normal levels. Successful transplants have been recorded and one in particular was reported to be functioning two years after implantation[83]. Recently, more work has been done in the field of magnesium metabolism and cases of tetany which were unresponsive to the usual therapy responded to magnesium sulfate. It is felt that some cases will show this as a result of hypomagnesemia rather than hypocalcemia[1].

In this series of 23 surgical and two autopsy cases, there were nine known deaths which are outlined in Table IV. It would seem that renal complications are to be feared most of all. There was one unsuccessful operation which has been mentioned. Follow-ups in 15 patients not known to be dead, range from zero time to six years and all patients about whom information is available have been relieved of the majority of their constitutional, bone, gastrointestinal, and renal symptoms. One patient with hypertension had a cerebrovascular accident eight months after operation and this patient and two others who have been followed for one to four years have evidence of progressive renal damage. Of ten patients with an elevated NPN preoperatively, there was only one patient whose NPN fell to normal postoperatively, and that was the patient who had manifestations of acute hyperparathyroidism. Five patients with severe bone disease had x-ray evidence of improvement from four to seven months after operation.

Serum determinations were available on 20 patients who were successfully treated and the findings are fairly characteristic. The average

postoperative serum calcium was 9.75 milligrams percent and the average serum phosphorus was 3.63 milligrams percent. Four patients took from three to five months to attain normal serum calcium levels although the others achieved this within 24 hours. Three patients had somewhat elevated serum phosphorus levels after surgery but these were the results of single determinations and since no further follow-up was possible, no comment can be made about this. Six patients had postoperative determinations of alkaline phosphatase, and in four of these the levels were higher in the postoperative period, probably as a result of increased reconstructive activity in bone. Sixteen patients had information available with respect to symptoms of tetany. Five patients had no symptoms whatsoever. Eight had slight transient symptoms of tingling of the hands and feet, nervousness, and transient Trousseau and Chvostek signs. Only three patients had severe tetany, and all had evidence of severe bone disease. One of the latter three patients who had a carcinoma removed also had recurrent attacks of pancreatitis postoperatively, a phenomenon which has been noted before in parathyroid carcinoma patients[67].

There are lessons to be learned from a study of the postoperative course of these patients. First, neck dissection should be done with extreme care to avoid recurrent nerve paralysis and destruction of remaining parathyroid tissue. Second, most patients will improve after operation except those with severe renal disease and this should give us the

incentive to make earlier diagnoses. Third, extreme care should be taken in those with severe renal disease since they may be thrown into renal failure by surgery. Fourth, severe tetany does occur and it should be watched for and rapidly treated. Mild tetany is to be expected in practically all cases.

TABLE IV.

DEATHS - 9 cases

	Causes	Length of time after surgery
1.	Bronchopneumonia	18 days
2.	Malignant hypertension and renal failure	2 months
3.	Dissecting aortic aneurism	autopsy case
4.	Renal failure	autopsy case
5.	Renal failure	8 days
6.	Left lower lobe pneumonia	2 days
7.	Hypertension and congestive heart failure	6 years
8.	Pneumonia, hypertension, pyelonephritis	10 years
9.	?Septicemia or aspiration	12 hours

Summary and Conclusions

1. Some information concerning the history and pathophysiology of hyperparathyroidism is discussed.

2. The natural history of primary hyperparathyroidism is outlined with relation to 25 proven cases seen at the Yale-New Haven Medical Center. The sex incidence in this study was about equal and the average age was 48 years. Those with bone disease had symptoms a year longer than those with only renal disease. Renal symptoms and hypertension were the most common manifestations followed by skeletal symptoms and general symptoms such as weight loss, fatigue, weakness, constipation and arterial calcification. Skeletal symptoms are decreasing in incidence as diagnoses are being made earlier. One case of acute hyperparathyroidism is discussed. Gastrointestinal symptoms were early manifestations and it is hoped that a knowledge and awareness of these and other early signs will lead to early diagnosis. Considering the number of diagnoses made in recent years, it is probable that an appreciable number of cases may have been overlooked.

3. A number of the various diagnostic tools are discussed. A high index of suspicion and careful attention to the details of history are important along with frequent follow-ups. Radiologic examinations give information about the development of the disease and, in this series, neck studies were helpful in six out of 13 instances. Of the laboratory

tests, serial serum calcium and phosphorus determinations are still the most specific by far. Other tests are described but limited experience allowed only limited evaluation. It is thought that the percent TRP test may be of some value but a combination of tests is even better. Information is also presented on six cases in which the diagnosis was probable but not proven.

4. Pathologic studies on 24 cases are presented. Nineteen patients had single adenomas and three had double adenomas. Two patients had single Wasserhelle adenomas and all the rest were chief cell types. One patient each had generalized hyperplasia and carcinoma. The average weight of the adenomas was 3.2 grams with 25 percent of these being one gram or less and thus being hard to find. Nine of the 24 patients had palpable pathology.

5. Medical, radiologic and surgical methods of treatment are discussed. Surgery is the only effective method and stress is placed on careful technique taking details of the embryology and anatomy of the parathyroid glands into account. Over 95 percent of cases should be cured by a cervical approach. Seventy-one percent of adenomas occurred in the inferior glands and there was no right or left-sided predominance. Reasons for failure are discussed and rigid adherence to proper technique is most important in this respect. Some newer methods of locating the pathology are discussed but not enough experience has been gained to evaluate them. Treatment of acute hyperparathyroidism is

also discussed and stress is placed on recognition of this process and rapid initiation of treatment.

6. The postoperative "natural history" is discussed. Most patients improve with disappearance of practically all symptoms, return of serum values to normal levels, and repair of bone disease. Renal disease progresses; therefore, it is necessary to diagnose and treat before permanent renal damage occurs. Most patients experience slight symptoms of tingling and nervousness postoperatively, but a few with severe bone disease will experience severe tetany which must be treated rapidly. Again, stress is placed on careful handling of tissues. Complications included five cases of progressive renal disease and failure, three cases of severe tetany, two cases of vocal cord paralysis, and one case of pancreatitis in the patient with carcinoma.

7. Finally, our aims for the future should include:

a. An awareness of the existence of this disease and of its symptoms with the aim of catching it in its early stages,

b. The development of more specific methods of early diagnosis,

c. The development of better surgical techniques and methods of locating the offending pathology, and

d. The avoidance of postoperative complications.

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